

Illustration

The graph below illustrates the game of animal testing. Let's assume 6 different horses are running six different races. Let's also assume there are 6 different tip sheets people can purchase, each promising to pick the winner. The graph below illustrates the results.

When the tip sheets are considered together, they predicted all the winners. But this is disingenuous as the race goers can only bet based on one tip sheet. So what we should really evaluate is how the sheets did individually. When using that criterion, the tip sheets predicted 7 out of 36 winners. Not much better than chance.

The next graph brings relates this example to our discussion of drug testing.

Race #	Horse name						Tip Sheets					
							Winner's	BestBet's	Happyday's	Gold's	Trifecta's	A+++
1	Apple	Bertha	Charlie	Devil	Everready	Fastest	Apple	Charlie	Bertha	Bertha	Devil	Apple
2	GoBoy	Hell's Fury	Ichabod	Jumper	Kaloza	Loper	Kaloza	Hell's Fury	Kaloz	Loper	Loper	GoBoy
3	Minute Man	Noshow	Out Of Here	Prancer	Quest	Racer	Quest	Racer	Out Of Here	Prnacer	Quest	Quest
4	Stoned	Turn It On	Unbridled	Victory	WinIt	X-Bet	WinIt	WinIt	Stoned	Victory	WinIt	WinIt
5	Yazoo	Zeke	Accelerate	Break Away	Close The Gap	Diablo	Diablo	Zeke	Diablo	Diablo	Close The Gap	Zeke
6	Explode	Frank	Gertrude	Henry	Ivan	Jay	Ivan	Ivan	Ivan	Jay	Jay	Ivan

		Animal Model (Tip Sheets)					
DRUG (Horse race)	Human (Winner)	Cat	Dog	Mouse	Monkey	Guinea pig	Rabbit
Thalidomide	Phocomelia	SAFE	SAFE	SAFE	Variable		Phocomelia
Penicillin	Cure	Cure	Cure	Cure	Cure	Kills	Rapid metabolizer
Alzheimer's vaccine	Worsens disease			SAFE	SAFE	SAFE	SAFE
Vioxx	Heart attack Strokes		SAFE	SAFE			
HRT	Cancer, Dementia, Heart disease		SAFE	SAFE	SAFE		
Fen-phen	Heart valve abnormalities		SAFE	SAFE			
Opren	DEATH			SAFE	SAFE		
Flosint	DEATH			SAFE	SAFE		
Fenclozic acid	Liver failure	SAFE	SAFE	SAFE	SAFE	SAFE	SAFE

Here we see that depending on the drug, sometimes a rabbit reacted the same way as humans and other times the rabbit reacted differently. The same is true of *all* the other species.

The point is, when the vested interest groups say that animal models predicted adverse drug reactions, what they mean is that taken collectively, one can usually find an animal that reacts like a human. The problem of course is that we cannot know prospectively *which* animal is human-like until we know how humans react. Therefore the animal tests are not useful. Their actual effectiveness in predicting drug response is more like 20%.

So, how should drugs be tested?

Pharmacogenomics is the application of knowledge gained from the Human Genome Project and other studies of genetics to the field of drug discovery. The goal is to link genetic variation with pharmacologic properties. For example, by isolating which gene is involved in the side effect aplastic anemia, physicians can test a patient for this gene before administering a drug.

Gene discovery will also allow scientists to design a drug to interact with the specific gene causing a disease. By isolating the gene involved in metabolizing a drug, scientists can predict if the patient will metabolize a drug slowly or quickly, thus affecting what dose the patient needs.

This will change the way drugs are discovered, developed, marketed, and prescribed. It will also change the way drugs are approved. Clinical trials need no longer be conducted on all types of humans, only those for whom the drug was designed--those who have the correct genetic profile for the drug. This will mean smaller, cheaper, and more effective clinical trials. This will increase the number of drugs on the market, and possibly bring back old drugs that were recalled due to severe adverse side effects.

What is needed in ADMET studies is pharmacogenomics. By classifying patient populations based on their response to drugs and on their drug metabolizing enzymes (DMEs), drugs can be prescribed in a safer more effective fashion.

Patients who have the gene or protein that causes an adverse side effect can be given a different drug, and patients who metabolize the drug slower or faster can have their dosage schedule altered accordingly. Some of the knowledge and technology needed to thus classify patients has been available for over 2 decades.

Physicochemical measurements such as ionizability (pKa) and lipophilicity (log P or log D) can be used to predict how the drug will be absorbed from the gut. *In vitro* tests utilizing Caco-2 cells from human colon carcinoma cells, can be used to predict absorption and secretion of drugs in the small intestine.

There are myriad tests that are far superior to animal tests.

So why does animal testing for medications continue?

Animal testing for medications is tradition and is accepted by a naïve society. The entire system is geared for it, and it is cheap and fast compared to human trials. A drug company can speed the drug to market based on animal tests while human tests take much longer. They also get liability protection.

The government is on board with this. It is difficult to change government regulations especially when Industry *likes* them.

Finally, the testing process keeps people employed, and many people have a direct or indirect vested interest in the process.